EXHIBIT C

PATENT
SCRIP1100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	M. Von Herrath	Art Unit:	1636
Application No.:	09/336,672	Examiner	W. Sandals
Filed:	June 17, 1999		
Title:	COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF AUTOIMMUNE DISORDERS		

#22

Commissioner of Patents
Washington, D.C. 20231

DECLARATION OF APPLICANT UNDER 37 C.F.R. §1.131

Sir:

I, Matthias G. von Herrath, M.D., the sole inventor of the above-identified application, do hereby declare and state that:

1. I am familiar with the content of the above-identified application.

2. I am aware that claims 1-3, 5, 7-14, 16-24 and 26-39 have been rejected under 35 U.S.C. § 103 for allegedly being unpatentable over the disclosure of Jingxue Liu et al. (*Gene Ther Mol Biol* 3:197-206, 1998; hereinafter "the Liu article") in combination with the disclosure of PCT publication WO 97/46253.

3. The claimed invention was conceived and reduced to actual practice by me in the United States as sole inventor prior to the publication date of the Liu article, as supported by the evidence which follows:

At the time the present invention was conceived and reduced to actual practice, I was the leader of the research team that performed the experiments set forth in the Examples of the above patent application, which experiments were completed in laboratories of The Scripps Research Institute, Department of Neuropharmacology, Division of Biology in La Jolla, California prior to the publication date in 1998 of the Liu article. In support of this statement are attached true

copies (with only the dates redacted) of pages from The Scripps Research Institute Technology Disclosure document and an unpublished short manuscript entitled "DNA immunization to prevent autoimmune diabetes" naming me as co-author that was prepared for publication in the technical journal *Nature Medicine* prior to the date of publication in 1998 of the Liu article.

Thus, I maintain that the subject matter contained in the above-identified application was conceived and actually reduced to practice by me, in the United States, prior to the date of publication in 1998 of the Liu article. Further, I was diligent from the time of conception of the invention until the time of filing the above-identified patent application.

3. Furthermore, the co-authors Bryan Coon, Ling-Ling An, and J. Lindsay Whitton, named in the article entitled "DNA immunization to prevent autoimmune diabetes" are not co-inventors of the present invention. These named co-authors contributed to the research effort described in the article, but are not co-inventors of the subject matter of the present invention, as defined by new claims 40-60, because they did not contribute to conception of the invention described in the subject patent application.

4. I further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1/15/2002
Date

Matthias G. von Herrath, M.D.

Attachments
Technology Disclosure (3 pages)
Manuscript (3 pages)

The Scripps Research Institute

TECHNOLOGY DISCLOSURE

DISCLOSURE NUMBER: 98-170 DATE:_____

The purpose of this disclosure is to document and identify your technology/discovery. It is intended to help us meet our government reporting obligations, give our industrial sponsors a means of determining the commercial potential of the technology and our attorneys a document from which to assess its patentability.

TITLE/SUBJECT/BRIEF DESCRIPTION OF INVENTION/DISCOVERY:

Use of recombinant DNA vaccination to induce/activate regulatory cells that prevent autoimmune diseases

INVENTOR(S) NAME AND HOME ADDRESS	CITIZENSHIP	PHONE NO.
1.) Matthias G. von Herrath, M.D. 4-9602	USA	619.481.9712
2.) 14295 Minorca Cove		
3.) Del Mar, CA 92014		
4.)		

Has the discovery been described (orally or in writing) to anyone other than a TSRI employee or coinventor? If so, to whom and date:_____

Have any specific materials (e.g., peptide, protein, cells, antibodies, DNA preparations, etc.) been distributed to anyone other than TSRI employee or coinventors? YES (NO)

Disclosure No. 98-170

Has a PAPER or ABSTRACT describing this discovery been submitted for publication? YES (NO)
If so:

Projected Journal/Meeting: Nature Medicine, 1/1999 (In preparation, not submitted, no abstract)

Projected Date:_____ TSRI Manuscript No.:_____

FUNDING SUPPORTING THIS INVENTION:

GOVERNMENT FUNDING? (YES) NO

IF YES: Agency: NIH NIAID R01 AI44451; NIH NIDDU R29 DK51091;

Grant Number(s): JDFI CDA 296120

Was the GCRC used in developing this INVENTION?

YES (NO)

PRIVATE FUNDING? YES (NO)

IF YES: Funding Source:_____

Invention is a (circle): Compound Device Diagnostic (New Use) Process

Were any materials obtained from an outside source, under a Materials Transfer Agreement (MTA), used in this research? YES (NO)

IF YES: Company:_____

Material(s):_____

Date of MTA:_____

INVENTOR(S) SIGNATURE(S): DATE:

Dr. M. v. Herrath

(Matthias v. Herrath)

PRINCIPAL CONTACT:

Investigator Name: Matthias von Herrath Telephone: 49602 Mail Drop: IMM6

Disclosure No.: 98-170

DESCRIPTION OF INVENTION:

As of my knowledge, my laboratory is the first one that used a recombinant DNA plasmid expressing a pancreatic self antigen to vaccine transgenic mice and successfully prevent autoimmune diabetes. We were able to show that this vaccination is effective through induction of regulatory cells, a finding which makes this approach very different and more effective and feasible than other previous DNA-vaccination strategies used to prevent autoimmune diseases. Thus, our tactic might be a highly useful tool to treat human autoimmune disorders, because only one self antigen from the autoimmune-target organ has to be expressed in the plasmid and a one-time injection given at the right time is sufficient. There are no side-effects and general immune function is not affected (see attached draft paper).

UTILITY: Treatment of autoimmune disorders with recombinant DNA plasmids expressing self-antigens.

ADVANTAGES (Particularly as relates to commercialization):

One-time shot; no side effects; easy to use; highly effective (so far in animal model)

CLOSEST KNOWN PUBLICATIONS:

9424

M.G. von Herrath, T. Dyrberg and M.B.A. Oldstone. J. Clin. Inv. 98:1324-1331, 1996.

M.G. von Herrath. Research in Immunology, 148:541-554, 1997.

M.G. von Herrath. Transpl. Proc., in press, 1998.

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DNA immunization to prevent autoimmune diabetes

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Background

DNA vaccination with plasmids expressing foreign microbial antigens is a well-established approach to induce protective anti-viral or bacterial immunity [ ]. After one-time or repeated intramuscular (i.m.) or intradermal injection(s) cellular and/or humoral immune responses to the desired microbial protein are mounted. Some of the activated cells become long-lived memory lymphocytes that upon re-encountering the same antigen (for example during infection with the respective virus or bacterium) are activated faster and expand more readily than naïve lymphocytes. However, in addition to their protective role during infections, lymphocytes can also have important regulatory functions. These become apparent, for example, when self-antigens are administered orally [ ]. In this scenario, depending on the antigen dose and precise protein sequence, self-reactive lymphocytes are induced in the gut [ ]. Such cells are capable of suppressing ongoing autoimmune destruction and prevent autoimmune disease when they home locally to a target organ under autoimmune attack, a process termed "oral immune tolerance" [ ]. Based on these facts, the goal of our present study was formed: We sought to investigate the potential of DNA-vaccination with islet self-antigens to induce regulatory lymphocytes and prevent autoimmune diabetes (IDDM). Such a therapy would constitute a safe and simple approach to protect pre-diabetic individuals at risk. We chose the well-established RIP-LCMV-NP mouse model for virally-induced IDDM, in which lymphocytic choriomengitis virus (LCMV) nucleoprotein (NP) is expressed as a "self" transgene in β-cells. Upon infection with LCMV, 90-100% of the mice develop diabetes mediated by CD4 and CD8 lymphocytes that eliminate the viral infection and, at the same time, react with the LCMV viral "self" protein expressed in β-cells. The model has two distinct advantages for such an investigation. First, the initiating self (viral-NP) antigen is known and autoreactive (anti-viral) lymphocytes can be tracked precisely. Second, oral administration of insulin has been demonstrated to prevent IDDM in this model, which is mediated by $CD4^{+}\alpha/\beta^{-}$ IL-4 producing regulatory cells reactive to the insulin B-chain [ ] that change the cytokine profile in pancreatic islets from Th_1 to Th_2 [ ].